Summary of Presentations from the 11th Targeted Therapies for Lung Cancer Meeting

Radiation Oncology

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Although one of the latter sections, a number of interesting concepts and ideas came out of the radiation oncology talks at IASLC 2011 in Santa Monica. The session was chaired by Everett Vokes of the University of Chicago and by Dr. David Johnson of UT Southwestern Medical Center at Dallas. The four speakers in order were Hak Choy of UT Southwestern Medical Center at Dallas, Michael O'Reilly from UT MD Anderson Cancer Center, Walter Curran of Emory University Medical Center, and Everett Vokes of the University of Chicago. The following summaries highlight the main themes of each talk and attempt to provide a framework for their critical importance to the clinical and biologic aspects of radiation oncology.

Summaries of Talks

The first talk, by Hak Choy, focused on combination therapies in the setting of Stereotactic Ablative Radiation (SABR). One of the recent important findings out of the radiation biology laboratories at UT Southwestern Medical Center (Chaitin Nirodi——both published and unpublished data) is the notion that EGFR mutant status goes far in potentially determining how sensitive non-small cell lung cancer (NSCLC) cells are to radiation therapy.[1,2] With an increasing emphasis on demonstrating that EGFR is involved in DNA repair along with its function as a modulator of mitogenic signals, it has become imperative to understand how mutant EGFR lung tumor cells may behave in unique ways. Nirodi's laboratory has shown that mutant EGFR cells are more sensitive to external beam radiation in comparison with wild-type EGFR tumor cells. This may be occurring because wild-type EGFR tumor cells may have some continued DNA repair capacity rendering them somewhat radiation resistant. On the contrary, mutant EGFR cells, acting similarly to cells treated with cetuximab, have less DNA repair capacity because of the lost EGFR function, and as a result, tend to respond to radiation effects.

Initially in his talk, Dr. Choy summarized what SABR is and described outcomes from the 2010 *JAMA* article demonstrating benefits of using SABR in inoperable patients with stage I/II NSCLC in a phase II study.[3] Subsequently, he provided a summary of the orthotopic lung tumor models available for mice and rats with an emphasis on UT Southwestern Medical Center's capacity to irradiate tumors at stereotactic doses with image guidance. He then went on to mention how SABR plus DNA PKC inhibitors in combination are more effective in promoting cell death when compared with fractionated radiation plus or minus these same inhibitors in preclinical evaluations. When combining SABR with EGFR inhibitors including cetuximab, the effects were most profound in lung tumor cell lines with mutant EGFR expression. It thus becomes more and more imperative to understand the nature of the EGFR mutations present in NSCLCs before deciding on optimal treatment approaches. Cetuximab's utility in the setting of combined modality therapy with radiation is highly dependent on not simply EGFR overexpression, but whether that overexpression is in the wild-type or mutant form. Ultimately, combining SABR with EGFR inhibitors for tumor cells overexpressing specific mutant EGFR forms maybe the most synergistic combination.

Michael O'Reilly expounded on another aspect of concurrent chemoradiation approaches, the use of antiangiogenic modulators and fractionated radiation. Over several years, the O'Reilly group has worked on multiple orthotopic mouse models to study radiation combined with angiogenesis inhibitors.[4] With respect to NSCLC, he presented preclinical data showing that cediranib works best when given with fractionated chemoradiation to block locoregional lung tumor spread to the mediastinum and distant spread. This block in angiogenesis leads to increased tumor apoptosis but no obvious difference in tumor or endothelial proliferative capacity. With respect to preclinical small cell lung cancer (SCLC) studies, combined use of doublet chemotherapy with fractionated radiation and cediranib or vandetanib led to increased tumor control but limited control of metastatic disease in the absence of cediranib. Finally, there was discussion of the toxicity associated with combined modality treatment in the thorax, specifically the elevated rate of tracheoesophageal fistulas in the setting of chemoradiation with avastin. A point was made that with the use of newer technologies, including proton radiation therapy and better image guidance, fewer of

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these events may occur when combining angiogenesis inhibitors with radiation and cytotoxic agents.

The concept of the next talk, by Walter Curran, was to describe the latest clinical advances with radiation and EGFR inhibitors/TKIs (tyrosine kinase inhibitors). Dr. Curran divided his talk into five sections—preclinical evidence or lack thereof for using TKIs with radiation, sequential chemoradiation-TKI trial results, concurrent chemoradiation-TKI results, possible role for these combinations in lower performance status patients, and combining TKIs with hypofractionation/SABR. Several preclinical studies using TKIs with radiation previously showed great synergy in effectuating NSCLC cell kill as far back as 2003. In subsequent sequential clinical trials including SWOG 0023 attempting to take advantage of this preclinical work, it was summarized that when comparing chemoradiation plus taxanes plus either gefitinib or placebo, the group receiving gefitinib had worse survival outcomes with increased toxicity.[5] When randomizing patients with NSCLC after chemoradiation straight to adjuvant erlotinib versus placebo, there were no differences in outcome.

There were till recently several ongoing concurrent trials including a phase I study at the University of Colorado and CALGB 30106 which were looking at induction chemotherapy (with gefitinib) followed by concurrent chemoradiation with gefitinib given throughout primary therapy and as maintenance for stage III NSCLC patients. The former study was discontinued because of the negative results of SWOG 0023. The 1-year overall survival (OS) for the latter study was 60%.[6] An Australian phase I/II study for stage III NSCLC patients has been evaluating increasing doses of paclitaxel with concurrent radiation plus ZD1839 and has shown a 3-year overall survival of 60% (Ball et al, ASCO 2007). A similar study at UNC has been evaluating induction chemotherapy followed by concurrent chemoradiation plus daily gefitinib with a dose escalation to 74 Gy.[7] Unfortunately, the median survival time (MST) for this study has been 16 months. Another phase I study by Choong et al.[8] has examined cisplatin/etoposide-based chemoradiation plus erlotinib and docetaxel consolidation to carboplatin/taxol-based induction followed by chemoradiation plus erlotinib and found no significant differences in outcomes from historical results. Study LCCC 0511 which is evaluating bevacizumab and erlotinib with induction and concurrent carbotaxol with 74 Gy thoracic radiation is still in accrual stage.

Finally, two other studies combining EGFR inhibtors/TKIs were described. CALGB 30605/RTOG 0972 looks at lower performance status patients and gives them induction carboplatin and abraxane followed by Erlotinib + 66 Gy thoracic radiation. This study is still accruing. Finally, a study submitted to CTEP is comparing standard fractionation radiation versus hypofractionation with TKIs. Ultimately, the jury is still out on combining EGFR TKIs with concurrent therapy. The early studies showed no benefit but the newer studies are yet to finish accruing.

The final talk of the session was by Everett Vokes who summarized clinical studies evaluating the roles of various radiation sensitizers. As per Dr. Vokes, the current highly relevant questions for stage III NSCLC include the sequencing, cycle number, and integration of systemic agents including targeted therapies with radiation. He started by describing combining pemetrexed, a potent antimetabolite, with concurrent radiation. He reinforced the notion that there is ample preclinical evidence which led to the supporting of pemetrexed in its relevance to multiple clinical trials. A phase I study from 2001 involved a dose escalation with pemetrexed and concurrent radiation for stage III NSCLC with no increased toxicity.[9] A CALGB phase II study with chemoradiation using pemetrexed plus carboplatin versus cisplatin has no new updates. CALGB 30407 compared carboplatin/pemetrexed/radiation with that same regimen plus cetuximab followed by more pemetrexed. A majority of patients were able to receive some maintenance cycles of chemotherapy with pemetrexed after the initial definitive treatment. The primary grades 3 to 4 hematologic toxicities similar in both arms were neutropenia and thrombocytopenia. There were 4% treatment-related deaths in each arm. Median OS was 21.2 months in the first arm and 22.4 months in the second arm. On subset analyses by histology, there was no difference in response or outcomes when comparing squamous or nonsquamous pathology. Finally, there was some description of the PROCLAIM study, in which one arm of patients will receive cisplatin/pemetrexed/radiation followed by pemetrexed × 4 cycles versus cisplatin/etoposide/radiation followed by a platinum doublet. The talk concluded with discussion of this study's continued accrual marks.

Future Directions

In general, this session highlighted the need for better combined modality therapy in the face of continued poor outcomes for stage III NSCLC. Several of the studies highlighted the role of targeting specific pathways in conjunction with either fractionated or stereotactic radiation in the hopes of optimizing loco-regional responses. A better selection of patients for the EGFR inhibitor studies based on molecular tumor profiles in conjunction with SABR may prove most efficacious.

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